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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Hiroaki Yamamoto
Serial No. : 09/305,390
Filed : May 5, 1999
Title : METHOD FOR PRODUCING OPTICALLY ACTIVE 4-HALO-3-HYDROXYBUTYRIC ACID ESTER

Art Unit : 1652
Examiner : R. Hutson

Commissioner for Patents
Washington, D.C. 20231

PRELIMINARY REMARKS

Applicant requests entry of the enclosed request for continued examination and consideration of the following remarks in support of the present claims. These remarks are in response to the Advisory Action mailed May 23, 2001, and final Office Action mailed November 7, 2000.

Claims 7-10, 12, 14 and 23 are pending and under examination. Applicant respectfully requests reconsideration of the present application.

The Advisory Action states that the rejections under 35 U.S.C. 112 have been withdrawn. However, claims 7-10, 12, 14, and 23 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Matsuyama et al. (U.S. Patent No. 5,559,030), in view of Peoples et al. (U.S. Patent No. 5,229,279) or Somerville (WO93/02187). Applicant will now address the issues raised by the pending rejection.

The present claims are drawn to a method for producing optically-active (S)-4-halo-3-hydroxybutyric acid ester from 5-halo-acetoacetic acid ester using a purified acetoacetyl CoA reductase. Applicants were the first to discover that acetoacetyl CoA reductase catalyzes this reaction, and with a high degree of stereospecificity.

CERTIFICATE OF MAILING BY FIRST CLASS MAIL

I hereby certify under 37 CFR §1.8(a) that this correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated below and is addressed to the Commissioner for Patents, Washington, D.C. 20231.

November 26, 2001
Date of Deposit

Lucille M. Begalka
Signature

Lucille M. Begalka
Typed or Printed Name of Person Signing Certificate

Matsuyama et al. describes generation of (S)-4-halo-3-hydroxybutyric acid ester from 5-halo-acetoacetic acid ester, but does not utilize a purified enzyme of any sort for this purpose, let alone a purified acetoacetyl CoA reductase. Instead, Matsuyama et al. used various microorganisms in the form of whole cells, culture supernatants, or cell extracts. For example, Matsuyama et al. discloses at col.8, line 27 that a culture of *Kluyveromyces* can produce the desired product with a high degree of optical purity. However, Matsuyama et al. fail to disclose that the *Kluyveromyces* enzyme catalyzing the reaction is an acetyl CoA reductase, as claimed in the present invention. In fact, the cited reference fails to identify *any* particular type of enzyme as responsible for the generation of (S)-4-halo-3-hydroxybutyric acid ester from 5-halo-acetoacetic acid ester, whether derived from yeast or from bacteria such as *Brevibacterium ammoniagenes* or *Escherichia coli* (see the present specification at page 4, lines 4-12).

The present claims are limited to use of acetoacetyl CoA reductase, which is an enzyme not previously shown to catalyze the conversion of 5-halo-acetoacetic acid ester into (S)-4-halo-3-hydroxybutyric acid ester. Even if one of ordinary skill reading Matsuyama et al. decided to substitute a purified enzyme for the cell cultures successfully used by Matsuyama et al., that person would not choose to use an acetoacetyl CoA reductase as required by the present claims, because, as previously noted, Applicants were the first to discover that acetoacetyl CoA reductase catalyzes the conversion of 5-halo-acetoacetic acid ester into (S)-4-halo-3-hydroxybutyric acid ester. Clearly this reference supplies neither motivation to use a purified acetoacetyl CoA reductase for this reaction, nor expectation of success if one were to attempt it.

The Examiner has combined Matsuyama et al. with either Peoples et al. or Somerville, citing the latter two references for their teachings about the cloning of acetoacetyl CoA reductase from various organisms. Each of these secondary references teaches that the cloned enzyme can be used to catalyze a step in the production of polyhydroxybutyrate (PHB) biopolymers having polyester backbones. (See abstracts of both references.) Neither reference suggests that the enzyme can be used to produce optically-active (S)-4-halo-3-hydroxybutyric acid ester, nor even that the enzyme can react with a halo acetoacetic acid ester at all. In fact, both secondary references are concerned solely with producing PHB biopolymers. There is no motivation in either Peoples et al. or Somerville to experiment with substrates that are not designed to be

incorporated into PHB biopolymers, and certainly no teaching that such experiments would have any likelihood of success.

Since the cited art supplies neither the requisite motivation nor the requisite expectation of success, the claimed invention cannot be said to be obvious in view of the art. Any attempt to combine the disparate teachings of Matsuyama et al. on the one hand, and either Peoples et al. or Somerville on the other, necessarily involves hindsight that was gleaned upon reading Applicant's own disclosure about the newly discovered activity of acetoacetyl CoA reductase. As the Examiner is well aware, such a hindsight reconstruction is not permitted under U.S. law. The motivation to combine must come from the references themselves, and not from the Applicant's disclosure. Withdrawal of the rejection is therefore respectfully requested.

Applicant submits that all claims are in condition for allowance. Filed herewith is a Petition for Automatic Extension with the required fee. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 11/26/01

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